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Influence of Adherent and Effective Antiretroviral Therapy Use on Human Papillomavirus Infection and Squamous Intraepithelial Lesions in HIV-Positive Women

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Abstract

Background—The impact of HAART on the natural history of human papillomavirus (HPV) remains uncertain following conflicting reports. Prior studies, however, did not consider patients' adherence to their regimen, or HAART effectiveness (viral suppression).

Methods—HIV-positive women (N=286) who initiated HAART during follow-up in a prospective cohort were assessed semiannually for HPV (by PCR) and SIL. Adherence was defined as using

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HAART as prescribed ≥95% of the time, and effective HAART as suppression of HIV replication. The prevalence, incident detection, clearance/persistence of HPV/SIL before versus after HAART initiation were compared (using women as their own comparison group).

Findings—HAART initiation among adherent women was associated with a significant reduction in prevalence (odds ratio [OR] 0.60 [95% CI 0.44–0.81];p=0.001), incident detection of oncogenic HPV (hazard ratio [HR] 0.49 [0.30–0.82];p=0.006), and decreased prevalence and more rapid clearance of oncogenic HPV-positive SIL (HR 2.35 [1.07–5.18];p=0.03). Effects were smaller among non-adherent women. The associations of HPV/SIL with HAART effectiveness were fairly similar to those with HAART adherence.

Conclusions—Effective and adherent HAART use is associated with a significantly reduced burden of HPV and SIL; this may help explain why rates of cervical cancer have not increased during the HAART era, despite greater longevity.

Keywords

HIV; human papillomavirus; HPV; HAART; SIL; cervical neoplasia

INTRODUCTION

Rates of cervical cancer and its precursors are significantly elevated in women with HIV/AIDS compared with the general population.[1–4] It has been speculated that these rates might increase further as HIV-positive women live longer through the use of highly active antiretroviral therapy (HAART).[5] By prolonging the lives of HIV-positive women, HAART may increase cumulative exposure to oncogenic human papillomavirus (HPV), the viral cause of cervical cancer, as well as permit longer HPV persistence, and the accumulation of somatic mutations and epigenetic changes that contribute to cervical carcinogenesis. Furthermore, HIV-positive women are entering, for the first time in sizeable numbers, the age-groups in which cervical cancer rates reach their peak.[6]

Conversely, HAART can partially restore immune competence. Host immune status is strongly associated with the incident detection and persistence of oncogenic HPV, as well as with precancerous cervical neoplasia, in HIV-positive women.[7,8] It is of clinical and public health significance, therefore, to determine whether and to what degree HAART mitigates the effects of HIV on the course of HPV-related disease. Unfortunately, prior studies of HAART and HPV / cervical neoplasia have had conflicting results.[9–16]

A clearer understanding of the relationship between HAART and HPV-related disease may have been obscured by the failure of prior studies to account for variations in patient adherence with HAART, and variations in the effectiveness of the HAART regimen being used (e.g., suppression of HIV replication). Furthermore, prior studies were often limited by concerns regarding “selection by indication”; that is, women who are started on HAART by their physicians may be different in various ways, including being more infirm and less vigorous, than those who are not started, even after controlling for laboratory values, such as CD4+ T-cell count.[17]

Because of the challenges in capturing factors related to the initiation of therapy, and in an attempt to minimize selection by indication, the current investigation involved a direct comparison of HPV / squamous intraepithelial lesion (SIL) rates before and after HAART initiation in women who started HAART during follow-up (using these women as their own comparison group). We then conducted formal analyses to assess the impact of patient adherence and HAART effectiveness on these outcomes.

MATERIALS AND METHODS

Study Subjects

The Women's Interagency HIV Study (WIHS) is an ongoing prospective cohort of HIV-positive (n=2800) and HIV-negative women (n=973) enrolled through similar sources at six sites (Bronx, NY; Brooklyn, NY; Chicago; Los Angeles; San Francisco; Washington, D.C.). Enrollment was initially conducted between October 1994 and November 1995, and a second recruitment cycle occurred in 2002. Details of the WIHS data collection and recruitment methods have been reported.[18] In brief, participants undergo a semiannual visit that involves an interviewer-administered questionnaire, including a photo-assisted history of medication use, and a physical/gynecologic examination with specimen collection, including a cervicovaginal lavage (CVL) for HPV DNA testing. Our current study was limited to the subset of HIV-positive women who initiated HAART during their enrollment in the WIHS and who had adequate HPV DNA data before and after starting HAART (see Statistical Methods).

Laboratory Methods

The HPV DNA assays have been described in detail elsewhere.[19] Briefly, HPV DNA was detected utilizing L1 degenerate primer MY09/MY11/HMB01 polymerase chain reaction (PCR) assays, [20] that could identify over 40 individual HPV types. Oncogenic HPV types were defined as HPV 16/18/31/33/35/39/45/51/52/56/58/59/68/82/ and 73, and other HPV types were considered non-oncogenic.[21]

Pap smears were collected using an Ayre spatula and an endocervical brush. All cervical cytology was centrally interpreted at Kyto Meridien Laboratories (New York, NY) using the 1991 Bethesda System criteria for cytologic diagnosis.[22]

Statistical Methods—The dataset consisted of semiannual follow-up of all HIV-seropositive women who initiated HAART while in the WIHS. Because subjects acted as their own comparison group, though, the analysis was limited to individuals with adequate data before and after initiation of HAART. Specifically, the analysis was conducted amongst women who had at least 2 semiannual visits during the 2.5 years just prior to HAART initiation and at least 2 semiannual visits during the 2.5 years immediately following HAART initiation, with censoring once a woman missed more than a single visit. Women who did not contribute adequate data to both periods were excluded.

These criteria restricted the number of women eligible for this study, and it was understood that the subcohort would not be representative of all women in the WIHS. The goal was internal consistency – to carefully assess the same women over time in the presence and absence of HAART. Indeed, approximately 650 HAART initiators entered the WIHS fairly close in time to when HAART became widely available in 1996 and, by definition, had insufficient "before HAART" data (i.e., < 2.5 years). Among those with earlier enrollment dates only 286 (37%) of the 783 HAART initiators had adequate data both before and after starting HAART to be included in the analysis of adherent/non-adherent HAART use. More specifically, compared with all other women who initiated HAART during follow-up, the 286 women we assessed were slightly older (median age 39 versus 37), more likely to be African American (61% versus 51%), and had a higher median CD4+ count (320 versus 262) – based on data at the visit prior to HAART initiation. Nonetheless, since women acted as their own control group the effect estimates should be an unbiased measure of the biologic impact of HAART on the burden of HPV/SIL within the subcohort.

HPV prevalence was defined as the fraction of positive results among women with adequate HPV tests (demonstrated by the amplification of β-globin in the assay). Incident HPV detection

was defined as a positive result for an HPV type that was not present at earlier visits. HPV persistence was measured as the time to clearance of an HPV type following its initial detection, with clearance defined as the first subsequent negative result. A more stringent definition of clearance based on two sequential negative result could not be used due to the limited data, but several prior WIHS studies[7,23,24] found that results were unchanged using either definition. Our analyses did, however, distinguish between HPV persistence following incident versus prevalent detection, which our group and others have found to be an important variable.

Consistent with prior studies,[25,26] "*Adherence*" to the HAART regimen was defined as self-reported use of HAART as prescribed ≥ 95% of the time. More specifically, adherent women were those who reported ≥ 95% adherence for at least two sequential visits starting within 12 months of HAART initiation, with censoring at the visit prior to a report of a lower degree of adherence. "*Effective HAART*" was defined as in other studies,[27] as a reduction in HIV RNA level by >90%, or to undetectable levels, in a woman who had detectable plasma HIV RNA prior to HAART initiation. The change in CD4+ count could not be incorporated in our definition of effective HAART because these levels can have high intraindividual variability during short follow-up periods[28,29] which, in our small dataset, would have made it difficult to study temporal relationships. We considered effective HAART users to be women meeting the above definition for at least two sequential visits starting within 12 months of HAART initiation, with censoring at the visit prior to a report of an HIV RNA level no longer meeting our definition. Using a more restrictive definition of effective HAART, namely, only undetectable HIV RNA levels, did not alter the findings (data not shown).

All women not categorized as adherent HAART users were considered non-adherent, and all subjects not categorized as using effective HAART were considered to be using ineffective HAART. We did not study additional intermediate levels of adherence or effectiveness because the size of the subcohort limited our ability to further stratify our data.

To assess the effects of adherent and effective HAART use on prevalence of HPV/SIL we employed random effects models. Incorporation of a random effect in our models controlled for the fact that the data involved repeated observations of the same women over time, as well as multiple different HPV types, and allowed estimation of the within individual difference of interest (i.e., HPV/SIL prevalence rates before and after HAART initiation). Random effects models are one of the two types of models commonly used to analyze repeated observations of the same subject[s] over time. The other type of models, called marginal models, assess between individual differences (e.g., between women using versus not using HAART – a comparison of two separate groups) instead of the type of within-individual comparisons of interest in the current study. Thus, random effects models are most appropriate for analysis of the current dataset.

Incident detection of HPV (time-to-event) and time to clearance was assessed using frailty models. These models were used instead of standard Cox proportional hazards models for time-to-event analyses, since frailty models incorporate a random effect to adjust for within subject correlation; they are the most commonly employed time-to-event method that permits the comparison of women to themselves (i.e., before and after HAART initiation). The time-to-event data in these models were most limited for analyzing incident SIL, since those analyses were by definition limited to individuals without prevalent lesions, and unlike the incident detection of HPV (which involved multiple HPV types) incident SIL had a single endpoint. The application of frailty models and mixed effects models to the study of HPV natural history data was recently reviewed.[30]

All models adjusted for treatment of cervical neoplasia using a time-dependent variable, and the CD4+ count at the start of each period (pre-HAART and HAART). Adjustment for

additional covariates had no impact on any of the findings in our study, including variables that were associated with risk of HPV and SIL in prior analyses; i.e., age, number of sexual partners within the past 6 months, cigarette smoking, race/ethnicity (data not shown).

Initial analyses were restricted to just the 5 year period (2.5 years before and 2.5 after HAART initiation) employed to select the subcohort, but this restriction did not change any of the findings in our study. Therefore, the results shown throughout this report include data from all visits of the subcohort (a total of 2,097 person-years of data).

RESULTS

Table 1 shows subject characteristics at the visit just prior to HAART initiation, stratified by HAART adherence. No associations were observed between adherence and age, race, CD4+ count, number of sex partners in the prior 6 months, or smoking. There were also no cross-sectional differences in the prevalence of HPV or cytologic abnormalities at the visit prior to HAART initiation.

We then compared oncogenic HPV prevalence rates before and after HAART initiation. The average prevalence of oncogenic HPV decreased 36% in adherent women (from 22% before to 14% after HAART initiation), and 12% in non-adherent individuals (from 24% to 21%, respectively). The changes related to HAART were more clearly and accurately reflected in our multivariate mixed effects models, adjusted for covariates (see Methods). Specifically, adherent women had a highly significant reduction in oncogenic HPV prevalence following their initiation of HAART (odds ratio $[OR]_{\text{after vs before}}$, 0.60 [95% confidence interval [CI], 0.44–0.81]; p=0.001), whereas non-adherent HAART use was not significantly associated with a change in oncogenic HPV prevalence (Table 2A). A direct comparison of rates in adherent versus non-adherent women after HAART initiation suggested an approximately 30% reduction in oncogenic HPV prevalence related to adherence ($OR_{\text{adherent vs non-adherent}}$, 0.70 [95% CI, 0.48–1.01]; p=0.06).

Adherent HAART use was also associated with a reduction in the incident detection rate of oncogenic HPV. Specifically, the rate of incident detection decreased 33% from a mean of 5.4 per 100 person-visits to 3.4 per 100 person-visits in adherent women, whereas in non-adherent women it decreased 9% from 6.1 per 100 person-visits to 5.6 per 100 person-visits. In multivariate frailty models, adherent HAART use (hazard ratio $[HR]_{\text{after vs before}}$, 0.49 [95% CI, 0.30–0.82]; p=0.006) but not non-adherent HAART use was associated with reduced incident oncogenic HPV detection, and the difference in incident detection rates between the two groups was significant ($OR_{\text{adherent vs non-adherent}}$, 0.49 [95% CI, 0.28–0.86]; p = 0.01).

For analysis of HPV clearance the data proved too limited to study oncogenic HPV alone. Therefore, we studied clearance of any HPV (oncogenic and/or non-oncogenic HPV types) and found that adherent users had marginally greater clearance of any HPV after compared with before HAART ($HR_{\text{after-vs-before}}$ 1.28 [0.99–1.66];p=0.06), whereas there was no relation with non-adherent HAART use ($HR_{\text{after-vs-before}}$ 1.05 [0.86–1.29];p=0.63).

Table 2B shows the relationship between adherent HAART use and SIL. Our major endpoint was oncogenic HPV-positive SIL (oncHPV+ SIL), lesions that are thought to have potential to result in tumors. Adherent users had a significant reduction in oncHPV+ SIL prevalence after HAART initiation ($OR_{\text{after-vs-before}}$ 0.40 [0.18–0.88];p=0.02), that was non-significantly greater than the reduction in non-adherent patients ($OR_{\text{adherent-vs-non-adherent}}$ 0.68 [0.25–1.80];p=0.40). Although incident detection of oncHPV+ SIL was not significantly associated with HAART use, there was a significant relation of adherent HAART use with the rate of oncHPV+ SIL clearance ($HR_{\text{after-vs-before}}$ 2.35 [1.07–5.18];p=0.03), that was significantly

greater than the oncHPV+ SIL clearance rate observed among non-adherent women ($HR_{adherent\text{-}vs\text{-}non\text{-}adherent}$ 3.75 [1.43–9.88];p=0.007).

Table 3 shows the characteristics of the subcohort at the visit just prior to HAART initiation, stratified by HAART effectiveness (i.e., whether or not HIV RNA levels were reduced >90% or to undetectable levels). The sample size is slightly smaller (n=254) than for the analysis of HAART adherence due to missing data. No significant differences were observed in this cross-sectional comparison. However, those with effective HAART (65%) were on average more likely than those with ineffective HAART (35%; P<0.001) to report having been adherent during follow-up (and vice versa, in 65% of those who were adherent users HAART was effective).

The average prevalence of oncogenic HPV decreased 20% in patients using effective HAART (from 20% before to 14% after HAART initiation), and did not decrease but actually increased slightly from 22% to 24%, respectively, in those using ineffective HAART. In multivariate models effective HAART was marginally associated with reduced oncogenic HPV prevalence ($OR_{after\ vs\ before}$, 0.71 [95% CI, 0.50–1.02]; p=0.06), and significantly associated with the prevalence of any HPV ($OR_{after\ vs\ before}$, 0.72 [95% CI, 0.60–0.88]; p=0.002) (Table 4A). The incident detection of oncogenic ($HR_{after\ vs\ before}$, 0.62 [95% CI, 0.38–1.02]; p=0.06) and any HPV ($HR_{after\ vs\ before}$, 0.64 [95% CI, 0.46–0.92]; p=0.005) were also very similar in their associations with effective HAART use.

Ineffective HAART, in contrast, while having a marginal association with oncogenic HPV prevalence in multivariate models ($OR_{after\ vs\ before}$, 0.79 [95% CI 0.50–1.02]; p=0.06), had no associations with incident detection of oncogenic HPV or with prevalent/incident detection of any HPV. Clearance of any HPV was not associated with either effective or ineffective HAART.

Table 4B shows the relationship between HAART effectiveness and SIL. The findings were fairly similar for both oncHPV+ SIL and any SIL, but only the results for any SIL, with its greater number of endpoints, reached statistical significance. Specifically, effective HAART was non-significantly associated with reduced prevalence of oncHPV+ SIL ($OR_{after\text{-}vs\text{-}before}$ 0.47 [0.19–1.16];p=0.10), and significantly associated with any SIL ($OR_{after\text{-}vs\text{-}before}$ 0.45 [0.25–0.80];p=0.007), whereas ineffective HAART use was not associated with prevalence of any SIL or oncHPV+ SIL. The data were more limited for the analysis of incident SIL (see Methods), and while the observed HRs were in the expected (inverse) direction, only the relationship between ineffective HAART and the incident detection of any SIL reached significance. SIL clearance, however, like SIL prevalence, had a significant association with effective ($HR_{after\text{-}vs\text{-}before}$ 2.48 [1.10–5.61];p=0.03) but not ineffective HAART ($HR_{after\text{-}vs\text{-}before}$ 1.26 [0.53–2.99];p=0.60).

DISCUSSION

The effects of HAART on HPV infection and cervical neoplasia in HIV-positive women have remained uncertain.[9–16] The current study, therefore, employed several design features intended to help accurately measure changes in the natural history of HPV and cervical neoplasia related to HAART use. Most notably, our investigation focused on a single group of women enrolled in a long term cohort, all of whom started HAART during follow-up (instead of the more common practice of comparing two separate groups, HAART users and non-users), and then assessed rates of HPV infection and cervical neoplasia before and after HAART initiation. By using HAART initiators as their own comparison group, the study could more directly estimate the effects of HAART (i.e., results in the same women in the presence/absence of HAART), while minimizing concerns regarding selection by indication; i.e., the possibility

of bias due to the fact that women who are started on HAART by their physicians are often sicker than those who are not started. Furthermore, the current study was the first, to our knowledge, to consider whether subjects were adherent with their HAART regimen, and whether their HAART regimen was effective in suppressing HIV replication.

Our results suggest that the burden of HPV and SIL is primarily decreased when patients are adherent with their HAART regimen, or there is strong evidence that the HAART is effective against HIV. Specifically, HAART initiation amongst adherent women was associated with a significant reduction in the prevalent and incident detection of oncogenic HPV, as well as decreased prevalence and more rapid clearance of oncHPV+ SIL. Even in these adherent women, though, these associations were of moderate size, and perhaps because of this, it is notable that not every expected result was observed (e.g., the incidence of SIL was not lower among adherent compared with non-adherent women). However, the effects of HAART initiation were generally smaller and non-significant among non-adherent women. Fairly similar associations between HPV/SIL and effective versus ineffective HAART use were also observed.

The protective biologic effects of HAART against HPV/SIL could represent an important countervailing influence to the risk of cervical cancer related to longer patient survival with HAART. As mentioned, by prolonging the lives of HIV-positive women, HAART may increase cumulative exposure to oncogenic HPV, and allow accumulation of somatic mutations and epigenetic changes that can lead to cervical oncogenesis. Our data may help explain why despite the greater survival of HIV-positive women, cancer registry data have so far failed to detect an increase in age-specific cervical cancer rates among women with HIV/AIDS during the HAART era.[15,16] At the same time, the moderate strength of these protective effects may help explain why age-specific cervical cancer rates have also not discernibly decreased.

However, even if age-specific cervical cancer incidence rates remain stable, the overall burden of cervical cancer in the HIV-positive population is still likely to increase as this population continues to age, since older women have higher rates of cervical cancer. This could especially impact African American women since they represent a disproportionately high fraction of HIV-positive patients, and their age-specific cervical cancer rates are considerably higher than those of Caucasians.[31]

Lastly, our results may help explain the variability in the findings between earlier studies of HAART and HPV/SIL. That is, HAART adherence and effectiveness should be considered in measuring the full biologic impact of HAART on HPV and cervical neoplasia. Differences in the results of prior studies, therefore, could reflect population differences in patient adherence, and/or HAART regimens and their effectiveness.

This investigation has several limitations that must be recognized. While our results are most likely internally consistent (e.g., reflective of the subcohort acting as its own comparison group), our data may not be entirely reflective of the WIHS, or women in other settings/countries. Also, an analysis contrasting adherence and effectiveness using a composite exposure variable might have been informative, comparing, for example, pre-HAART to adherent/effective, non-adherent/effective, adherent/ineffective, non-adherent/ineffective. However, that was not feasible unfortunately because of sample size. Furthermore, intervention studies that compare subjects before and after an intervention are susceptible to period effects; albeit, in the current study this concern was mitigated by the fact that we largely observed the expected differences in HPV/SIL carriage between adherent and non-adherent women even though both groups had similar follow-up. Most importantly, while strongly suggestive, we can not be completely sure how these data relate to invasive cancer, since we only studied the natural history of HPV and SIL.

In summary, we found that effective and adherent HAART use was significantly associated with a reduced burden of HPV and SIL among HIV-positive women. These protective effects may help explain why age-specific cervical cancer rates have not increased despite the greater survival of HIV-positive women during the HAART era. However, the overall public health burden of cervical cancer in HIV-positive patients could grow as this population increasingly enters older age groups with higher cervical cancer rates.

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Table 1

Selected characteristics of Adherent and Non-adherent HAART users at the visit just prior to HAART initiation.

	HAART Adherence		
Characteristic	**No**	**Yes**	**P**
	N=142	N=144	
Age group			0.45**
<35 y	43 (30%)*	35 (24%)	
35–39 y	33 (23%)	43 (30%)	
40–44 y	37 (26%)	30 (21%)	
>=45 y	29 (20%)	36 (25%)	
Race			0.21
White	17 (12%)	28 (19%)	
Black	91 (64%)	82 (57%)	
Hispanic and Others	34 (24%)	34 (24%)	
CD4+ T-cell count (cells/mm^3)			0.24**
CD4>500	33 (23%)	32 (22%)	
200≤CD4≤500	77 (54%)	67 (47%)	
CD4<200	32 (23%)	45 (31%)	
Number of Male sex partners in the past 6 months			0.34**
0	37 (27%)	47 (33%)	
1 (married)	23 (17%)	19 (14%)	
1 (single)	55 (40%)	58 (41%)	
>=2	21 (15%)	17 (12%)	
Smoking status			0.10**
None	26 (19%)	31 (25%)	
Former Smoker	28 (21%)	35 (28%)	
Current Smoker <10 pack years	41 (31%)	30 (24%)	
Current Smoker >=10 pack years	39 (29%)	30 (24%)	
Any HPV, number of individual HPV types			0.21**
0	49 (40%)	57 (45%)	
1	40 (33%)	35 (29%)	
>1	34 (28%)	27 (23%)	
Oncogenic HPV, number of individual HPV types			0.61**
0	88 (72%)	90 (76%)	
1	27 (22%)	21 (18%)	
>1	8 (7%)	8 (7%)	
Any SIL			0.16**
No	83 (76%)	88 (83.81)	
Low Grade SIL	24 (22%)	16 (15.24)	

	HAART Adherence		
Characteristic	**No**	**Yes**	**P**
High Grade SIL	2 (2%)	1 (0.95)	
Oncogenic HPV-positive SIL			0.98
No	83 (76%)	88 (84%)	
Yes	26 (24%)	17 (16%)	

* Certain data were missing at baseline for selected patients, and percentages do not always add up to 100% due to rounding.

** Two-sided Cochran-Mantel-Haenszel test. All other *P* values were determined with the two-sided Pearson's chi-square test.

Table 2

Adherent HAART use and the prevalence, incident detection, and clearance of HPV and squamous intraepithelial lesions (SIL).

A. HPV Results

		Any HPV			Oncogenic HPV		
Outcome	**Adherence**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Prevalence	Adherent vs. Pre-HAART	0.82*	0.70–0.98	0.03	0.60	0.44–0.81	0.001
	Non-Adherent vs. Pre-HAART	0.83	0.73–0.95	0.007	0.86	0.67–1.09	0.20
	Adherent vs. Non-adherent	0.99	0.80–1.21	0.91	0.70	0.48–1.01	0.06
Incidence	Adherent vs. Pre-HAART	0.69	0.51–0.94	0.02	0.49	0.30–0.82	0.006
	Non-Adherent vs. Pre-HAART	1.03	0.83–1.29	0.78	1.01	0.72–1.42	0.94
	Adherent vs. Non-adherent	0.67	0.47–0.96	0.03	0.49	0.28–0.86	0.01
Clearance	Adherent vs. Pre-HAART	1.28	0.99–1.66	0.06	--**	--	--
	Non-Adherent vs. Pre-HAART	1.05	0.86–1.29	0.63	--	--	--
	Adherent vs. Non-adherent	1.22	0.91–1.64	0.19	--	--	--

B. SIL Results

		Any SIL			OncoHPV+ SIL		
Outcome	**Adherence**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Prevalence	Adherent vs. Pre-HAART	0.68	0.43–1.10	0.12	0.40	0.18–0.88	0.02
	Non-Adherent vs. Pre-HAART	0.67	0.39–1.13	0.13	0.58	0.32–1.08	0.09
	Adherent vs. Non-adherent	0.97	0.50–1.90	0.93	0.68	0.25–1.80	0.43
Incidence	Adherent vs. Pre-HAART	0.68	0.25–1.85	0.45	0.72	0.29–1.77	0.48
	Non-Adherent vs. Pre-HAART	0.37	0.15–0.90	0.03	0.51	0.23–1.16	0.11
	Adherent vs. Non-adherent	1.83	0.51–6.62	0.36	1.41	0.46–4.30	0.54
Clearance	Adherent vs. Pre-HAART	2.25	1.03–4.93	0.04	2.35	1.07–5.18	0.03
	Non-Adherent vs. Pre-HAART	1.75	0.93–3.32	0.08	0.63	0.29–1.34	0.23
	Adherent vs. Non-adherent	1.28	0.54–3.06	0.57	3.75	1.43–9.88	0.007

Abbreviations: 95% CI = 95% confidence intervals; HAART = highly active anti-retroviral therapy; OncoHPV+ SIL = squamous intraepithelial lesions (SIL) that test positive for at least one oncogenic HPV type (whether or not non-oncogenic HPV were also detected).

*All models adjusted for treatment of cervical neoplasia using a time-dependent variable, and the starting CD4+ count (as detailed in the text). Adjustment for additional covariates had no impact on any of the findings, including variables that were associated with risk of HPV and SIL in prior analyses; i.e., age, number of sexual partners within the past 6 months, cigarette smoking, race/ethnicity (data not shown).

** No results were obtained due to non-convergence of the statistical models.

Table 3

Selected characteristics and outcomes of Effective and Not-effective HAART users at the visit right before HAART initiation.

	Effectiveness		
Characteristic	**No**	**Yes**	**P**
	N=127	N=127	
Age group			0.43**
<35 y	42 (33%)	29 (23%)	
35–39 y	30 (24%)	38 (30%)	
40–44 y	25 (20%)	34 (27%)	
>=45 y	30 (24%)	26 (20%)	
Race			0.31
White	16 (13%)	25 (20%)	
Black	81 (64%)	75 (59%)	
Hispanic and Others	30 (24%)	27 (21%)	
CD4+ T-cell count (cells/mm^3)			0.17**
CD4>500	31 (24%)	20 (16%)	
200≤CD4 ≤500	62 (49%)	69 (54%)	
CD4<200	34 (27%)	38 (30%)	
Number of Male sex partners in the past 6 months			0.97**
0	34 (28%)	38 (31%)	
1 (married)	20 (16%)	17 (14%)	
1 (single)	54 (44%)	47 (39%)	
>=2	15 (12%)	20 (16%)	
Smoking status			0.61**
None	26 (22%)	25 (22%)	
Former Smoker	23 (19%)	32 (29%)	
Current Smoker <10 pack years	40 (34%)	25 (22%)	
Current Smoker >=10 pack years	29 (25%)	30 (27%)	
Any HPV, number of individual HPV types			0.99**
0	50 (44%)	40 (41%)	
1	35 (30%)	34 (35%)	
>1	30 (26%)	23 (24%)	
Oncogenic HPV, number of individual HPV types			0.34**
0	82 (71%)	73 (75%)	
1	24 (21%)	20 (21%)	
>1	9 (8%)	4 (4%)	
Any SIL			0.90**
No	75 (79%)	76 (79%)	

	Effectiveness		
Characteristic	**No**	**Yes**	**P**
Low Grade SIL	19 (20%)	18 (19%)	
High Grade SIL	1 (1%)	2 (2%)	
Oncogenic HPV-positive SIL			0.64
No	99 (93%)	98 (91%)	
Yes	8 (7%)	10 (9%)	

* Limited to those contributing data to the present analysis. Some data were missing at baseline for selected patients. Percentages do not always add up to 100% due to rounding.

** Two-sided Cochran-Mantel-Haenszel test. All other *P* values were determined with the two-sided Pearson's chi-square test.

Table 4

Effective HAART use and the prevalence, incident detection, and clearance of HPV and squamous intraepithelial lesions (SIL).

A. HPV Results							
		Any HPV			**Oncogenic HPV**		
Outcome		**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Prevalence	Effective vs. pre-HAART	0.72*	0.60–0.87	<0.001	0.71	0.50–1.02	0.06
	Ineffective vs. pre-HAART	0.89	0.77–1.03	0.13	0.79	0.62–1.01	0.06
	Effective vs. Ineffective	0.81	0.65–1.01	0.06	0.90	0.60–1.35	0.61
Incidence	Effective vs. pre-HAART	0.64	0.46–0.88	0.006	0.62	0.38–1.02	0.06
	Ineffective vs. pre-HAART	1.00	0.78–1.29	0.98	0.92	0.64–1.34	0.68
	Effective vs. Ineffective	0.63	0.44–0.92	0.02	0.67	0.38–1.19	0.17
Clearance	Effective vs. Ineffective	1.03	0.75–1.42	0.84	--**	--	--
	Effective vs. pre-HAART	1.16	0.88–1.52	0.30	--	--	--
	Ineffective vs. pre-HAART	1.12	0.89–1.41	0.34	--	--	--

B. SIL Results							
		Any SIL			**OncoHPV+ SIL**		
Outcome		**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Prevalence	Effective vs. pre-HAART	0.45	0.25–0.80	0.007	0.47	0.19–1.16	0.10
	Ineffective vs. pre-HAART	0.93	0.55–1.58	0.79	0.80	0.42–1.51	0.48
	Effective vs. Ineffective	0.48	0.23–1.01	0.05	0.59	0.21–1.71	0.33
Incidence	Effective vs. pre-HAART	0.71	0.37–1.36	0.30	0.75	0.30–1.85	0.53
	Ineffective vs. pre-HAART	0.44	0.21–0.94	0.03	0.48	0.18–1.25	0.13
	Effective vs. Ineffective	1.61	0.65–3.95	0.30	1.56	0.47–5.21	0.47
Clearance	Effective vs. pre-HAART	2.48	1.10–5.61	0.03	1.21	0.42–3.49	0.72
	Ineffective vs. pre-HAART	1.26	0.53–2.99	0.60	0.55	0.24–1.27	0.16
	Effective vs. Ineffective	1.97	0.70–5.53	0.20	2.20	0.62–7.73	0.22

Abbreviations: 95% CI = 95% confidence intervals; HAART = highly active anti-retroviral therapy; OncoHPV+ SIL = squamous intraepithelial lesions (SIL) that test positive for at least one oncogenic HPV type (whether or not non-oncogenic HPV were also detected).

*All models adjusted for treatment of cervical neoplasia using a time-dependent variable, and the starting CD4+ count (as detailed in the text). Adjustment for additional covariates had no impact on any of the findings, including variables that were associated with risk of HPV and SIL in prior analyses; i.e., age, number of sexual partners within the past 6 months, cigarette smoking, race/ethnicity (data not shown).

** No results were obtained due to non-convergence of the statistical models.